basis of Invitrogen Catalog citing production of g/l of protein. That may be good and well, but Applicants are not producing simple proteins such as those listed in Invitrogen Catalog, for example, enzymes, proteases and protease inhibitors, membrane proteins, antigens and regulatory proteins. Applicants are producing complex molecules which are entire and intact monoclonal antibodies. Clearly, Invitrogen can be used to express antibody **fragments**, probably in the rate of production which Examiner is citing. However, it is generally known and accepted in the art that prokaryots, eukaryots and a unicellular eukaryots namely, such as the baker's yeast, *Saccharomyces cervisae* and the methylotrophic yeast, *Pichia pastoris*, although able to produce intracellular and extracellular proteins, including antibody fragments, they are not able to express complex intact antibodies (Nature Biotechnology, 16:773 (1998), J. BioChem., 121:831 (1997), BioTechnology, 13:255 (1995), PNAS (USA), 85:8676 (1998)).

In order for *P. pastoris* to produce such intact complex antibodies in quantities as claimed, the method for their expression must have been developed and modifications of claim 1 must have been invented, tested and their efficacy determined.

The problem with expression of antibodies rests with their structural arrangement. Antibodies contain several fragments, which individually could possibly be expressed by Invitrogen Catalog method as individual fragments, but cannot be expressed as one protein comprising these fragments without modifications of the Invitrogen method by invention steps.

Antibodies (Monoclonal Antibodies: Principles and Practice, pp. 7-10, Ed. J. W. Goding, Academic Prep, Inc., London (1983)) (copy enclosed) are complex symmetrical molecules made up of two identical **glycosylated** heavy chains of molecular weight typically between 50,000 - 75,000 and two identical **nonglycosylated** light chain of molecular weight around approximately 25,000. The heavy chains are joined by disulfide bonds to each other and each light chain is joined by a disulfide bond to one heavy chain.

Each chain is further made up of a series of homology units of approximately 110 amino acids. Each homology unit contains one intra-chain disulfide bond between cysteine residues situated about 20 amino acids from each end.

Each homology unit is folded into a domain, which is a compact, globular structure containing large amounts of β-plated sheets. Antibodies are thus complex molecules built of the different domains. These domains are encoded by different genes, as seen in Figure C of Immune System, Color Atlas of Genetics, E. Passarge, Thieme Medical Publishers, Inc., New York (1995)). Thus, light chains which are lower molecular weight proteins comprising one variable and one constant region, are encoded for by different genes than the heavy chains, which are proteins comprising one variable, one hinge and three constant regions. Each region is encoded for by different V_H (variable), CH1, H, CH2 and CH3 genes for heavy chains.

Proteins which are conveniently expressed with Invitrogen are regular proteins encoded for by one gene and not complexity of

genes, each encoding one specific region of the antibody, which regions additionally need to be interconnected with each by way of disulfide bridges.

The above is just a brief description of complexity of the antibody molecule. Monoclonal antibodies additionally contain other distinguishing features, however, the above description is deemed to be sufficient for the purpose of illustrating the complexity of antibody molecule. No such complexity exists in a regular protein which can be easily expressed by the Invitrogen method and kits. Applicants maintain that the Invitrogen kit and method does not produce the complete intact and functional antibody as described above and that their (Applicants') method developed just for this purpose, does. Only if such a structure can be reproduced in its entirety, the antibody of the invention, which is complete, intact and functional antibody, is obtained. It is respectfully submitted that Invitrogen methods and kits do not produce this complex structure.

It is respectfully requested that Examiner reconsider his rejection on the basis of these remarks.

Respectfully submitted,

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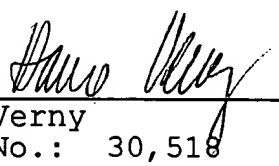

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